The role of arterial blood gas analysis (ABG) in amyotrophic lateral sclerosis respiratory monitoring

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There is still lack of consensus among different guidelines about the right timing for starting non-invasive mechanical ventilation (NIMV) in amyotrophic lateral sclerosis (ALS) [1-3]. The importance of spirometry as a reliable prognostic factor in ALS has been widely recognized; conversely, very few studies investigated the role of arterial blood gas analysis (ABG). Being respiratory failure the main cause of death in ALS, we aimed at investigating the role of ABG as proxy of Pulmonary Function Tests (PFTs) in a large cohort of ALS patients, identifying the best cut-off values for Forced Vital Capacity (FVC%), carbon dioxide (pCO2), carbonate (HCO3-) and standard base excess (SBE) to predict NIMV starting and survival.

We included 488 patients with concomitant ABGs, PFTs, and ALSFRS-r score, followed in the Turin ALS Center, resident in Piemonte and Valle d'Aosta, diagnosed between 2000 and 2015, excluding patients with severe pulmonary and kidney comorbidities. Descriptive statistic of the population is shown in Supplementary materials. Two-hundred and seventy-four patients (56.1%) underwent NIMV. Median time between ABG/PFT and NIMV initiation was 5.0 months (IQR 1.0-12.0). NIMV was started at a median FVC% value of 57.4% (IQR 44.2-73.6). Median overall survival after NIMV initiation was 225 days (IQR 104-491). Patients who did not undergo NIMV (N=214) were significantly older (68.6 years vs 64.9 years, $p<0.001$) and had a shorter overall median survival (2.3 years, IQR 1.5-3.5 vs 2.6 years, IQR 1.9-4.0, $p=0.003$).

ABG parameters showed a significant correlation with ALSFRS-r respiratory sub-score (for pCO2 $r= -0.301$; for HCO3- $r= -0.290$; for SBE $r= -0.291$; $p<0.001$ for all parameters) and with FVC% values (for pCO2 $r= -0.350$; for HCO3- $r= -0.345$; for SBE $r= -0.325$; $p<0.001$ for all parameters).

A significant decline in FVC% was recorded when pCO2 exceeded 42 mmHg, or HCO3- exceeded 26 mmol/L, or SBE exceeded 2 mmol/L (Table 1). Moreover, patients who had a single HCO3- increase (>26 mmol/L) showed reduced FVC% values; a further significant decline in FVC% was observed when both pCO2 and HCO3-were increased (Table 1). Therefore ABG parameters seem to predict pulmonary

function decline even when there is an isolated increase of HCO3- levels and also at pCO2 levels lower than the values commonly used to prescribe NIMV.

ROC curves showed that the most sensitive and specific cut-offs for starting NIMV within 3 months were: 70% for FVC%, 42 mmHg for pCO2, 26 mmol/L for HCO3-, and 2 mmol/L for SBE (see Supplementary material). Interestingly, the sensitivity and specificity of ABG measures were not influenced by neither type of onset (bulbar/spinal) nor the presence of bulbar dysfunction at time of ABG.

ABG/PFT values were predictive of death/tracheostomy only in patients who did not undergo NIMV. Risk of death/tracheostomy increased significantly by 83.0% when pCO2 reached 42 mmHg.

Taken together, our data indicate that the use of current guidelines for NIMV initiation could lead to a delayed treatment of respiratory failure in ALS patients, since we found a significant increase in death risk already when pCO2 blood levels were above 42 mmHg and FVC values dropped below 80%. Moreover, the current values of pCO2 and FVC% used for NIMV indication have a reduced sensitivity for NIMV starting within 3 months in comparison with cut-offs of 42 mmHg for pCO2 and of 80% for FVC%.

HCO3- elevation alone without significant pCO2 elevation occurred in about 25% of our patients, being a day-time marker of nocturnal hypoventilation (NH). NH is the first sign of respiratory failure in neuromuscular disorders [4] and one of the most frequent sleep disturbances in ALS, which is sometimes underestimated [5]. The frequency of respiratory symptoms did not differ between patients with normal ABG and those who showed a single HCO3- increase. Respiratory symptoms became more common only when both pCO2 and HCO3- increased (dyspnea in 53.1% and orthopnea in 42.0% of cases; $p<0.001$ for both). Based on these data, NH is a frequently asymptomatic entity, associated with a high risk for starting NIMV at 3 months (increase of HR by 54.7% and 45.9% when HCO3- and SBE were above 26.0 mmol/L and 2.0 mmol/L, respectively). As a compensatory mechanism, HCO3- elevation is related to a respiratory drive reduction with consequent worsening of hypercapnia. Current guidelines do not consider

blood HCO3- levels as a criterion to start ventilation [1,2,3]. According to our findings, after excluding any metabolic cause, we suggest that ALS patients could benefit from NIMV also in presence of an isolated increase of blood HCO3-/SBE levels.

Survival analysis confirmed our data: patients with normal pCO2 and HCO3- values at ABG survived longer than patients with normal pCO2 and increased HCO3- (1.39 years, IQR 1.23-1.55 vs 0.87 years, IQR 0.73-1.02; $p<0.001$) and patients with increased pCO2 and HCO3- levels (0.75 years, IQR 0.60-0.90; $p<0.001$, see Supplementary material).

The clinical-based retrospective nature of our study did not allow us to investigate other different PFTs, that have been proposed for respiratory function monitoring, such as maximal inspiratory/expiratory pressure (MIP/MEP) and/or sniff nasal inspiratory pressure (SNIP). However, their use is less considered than FVC/SVC in respiratory assessment and particularly in clinical trials.

ABG, though being minimally invasive, is a sensitive, easy to perform, and inexpensive tool for monitoring respiratory function in ALS patients, and turned out to correlate with FVC. Unlike other PFTs, ABG does not require patient collaboration and is not influenced by bulbar involvement. Moreover, it can detect NH, a clinical condition which is frequently underestimated in patients with neuromuscular disorders.

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Author Contributions

Dr Manera had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Concept and design:* Manera, Torrieri, Calvo, Chiò. *Acquisition, analysis, or interpretation of data:* Manera, Torrieri, Moglia, Viglione, Daviddi, Matteoni, Solero, Palumbo, Vasta, Canosa, D'Ovidio, Focaraccio, Mattei, Mora, Calvo, Chiò.*Drafting of the manuscript:* Manera, Torrieri. *Critical revision of the manuscript for important intellectual content:* Manera, Torrieri, Moglia, Mattei, Mora, Calvo, Chiò. *Statistical analysis:* Manera, Torrieri, D'Ovidio. *Obtained funding:* Moglia, Mattei, Calvo, Chiò. *Administrative, technical, or material support:* Viglione, Daviddi, Matteoni, Solero, Palumbo, Vasta, Canosa, Focaraccio. *Supervision:* Mora, Calvo, Chiò.

Conflict of Interest/Disclosures

Conflict of interest: Dr Manera, Dr Torrieri, Dr Moglia, Dr Viglione, Dr Daviddi, Dr Matteoni, Dr Solero, Dr Palumbo, Dr Vasta, Dr Canosa, Dr D'Ovidio, Dr Focaraccio, Dr Mattei and Dr Mora report no conflicts of interest. Prof Calvo has received research grant from Cytokinetics. Prof Chiò serves on scientific advisory boards for Mitsubishi Tanabe, Roche, Biogen, and Cytokinetics.

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Table 1. Median FVC% values for different values of pCO2, HCO3- and SBE and for combined pCO2/HCO3- cut-offs. Comparison of FVC% values at modifying of each ABG parameter. Mann-Whitney U test comparing each ABG parameter range to the previous one (p value < 0.05 was considered significant and significant values are written in bold).

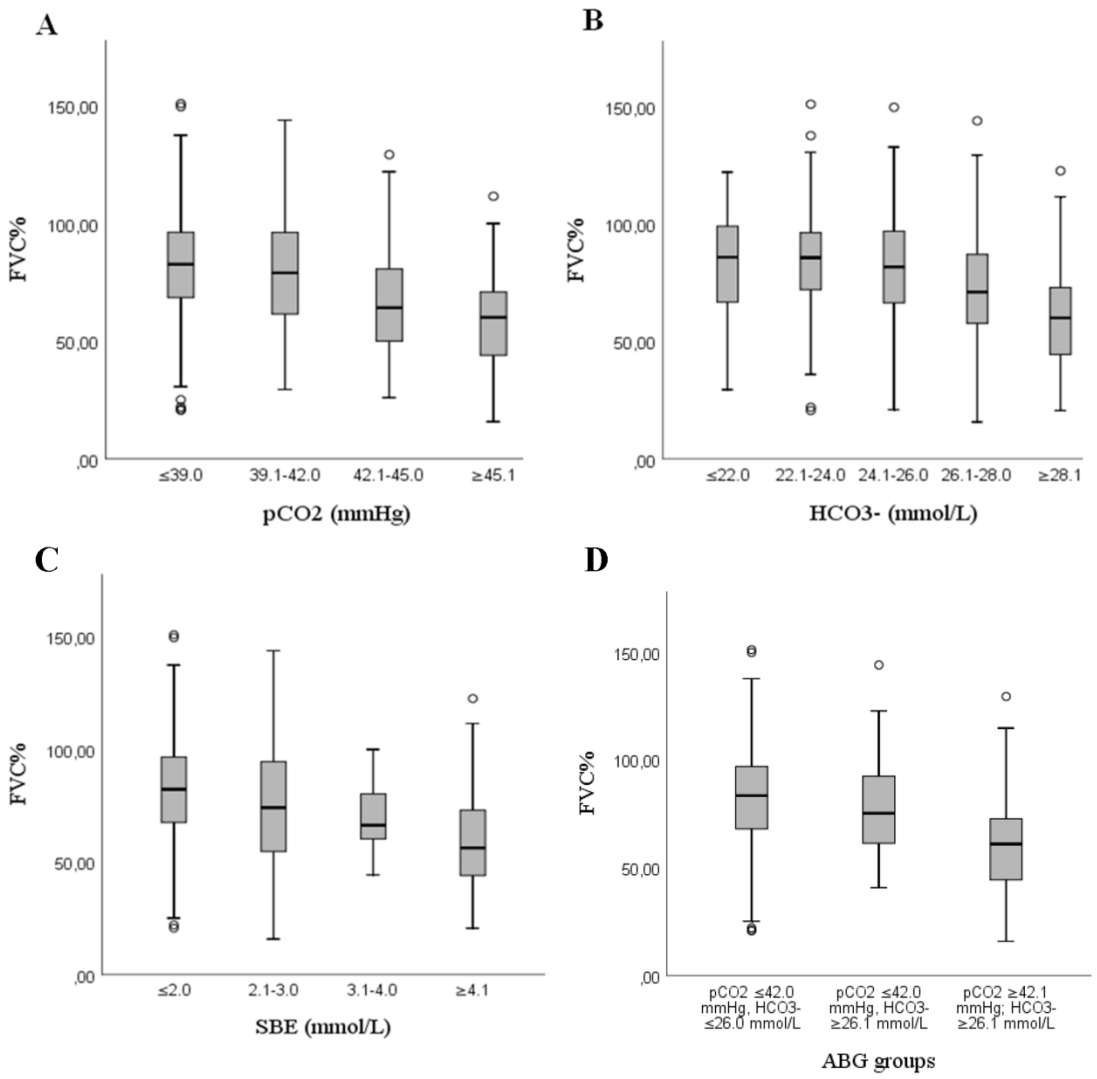
ABG parameter	FVC% (Median value, IQR)	p*
pCO2		
≤39.0 mmHg	82.7 (68.5-96.4)	
39.1-42.0 mmHg	79.0 (60.7-96.3)	0.205
42.1-45.0 mmHg	64.2 (49.6-81.3)	**0.007**
>45.0 mmHg	60.1 (43.2-71.0)	0.386
HCO3-		
≤22.0 mmol/L	85.7 (65.4-99.2)	
22.1-24.0 mmol/L	85.6 (71.8-96.4)	0.899
24.1-26.0 mmol/L	81.7 (66.2-97.3)	0.256
26.1-28.0 mmol/L	71.0 (57.6-87.2)	**<0.001**
>28.0 mmol/L	60.0 (44.4-73.2)	**<0.001**
SBE		
≤2.0 mmol/L	82.3 (67.4-96.7)	
2.1-3.0 mmol/L	74.1 (54.5-95.0)	**0.028**
3.1-4.0 mmol/L	66.3 (60.3-81.0)	**0.042**
>4.0 mmol/L	56.2 (43.7-73.5)	**0.014**
Combined pCO2/HCO3- (pCO2 cut-off = 45 mmHg)		
pCO2 ≤45.0 mmHg & HCO3- ≤ 26.0 mmHg	83.4 (67.9-97.0)	
pCO2 ≤ 45.0 mmHg & HCO3- > 26.0 mmHg	70.5 (56.0-88.0)	**<0.001**
pCO2 >45.0 mmHg & HCO3- > 26.0 mmHg	60.0 (42.8-71.0)	**<0.001**
Combined pCO2/HCO3- (pCO2 cut-off = 42 mmHg)		
pCO2 ≤ 42.0 mmHg& HCO3- ≤ 26.0 mmHg	83.4 (67.9-97.9)	
pCO2 ≤ 42.0 mmHg& HCO3- > 26.0 mmHg	75.2 (61.0-92.4)	**0.008**
pCO2 > 42.0 mmHg& HCO3- > 26.0 mmHg	60.9 (44.3-72.8)	**<0.001**

eTable 1. Demographic characteristics and ABGs/PFTs values. Patients who underwent NIMV vs patients who did not undergo NIMV. Differences of discrete and continuous variables were analyzed using the $\chi 2$ test and Mann-Whitney U test respectively. ΔALSFRS-R = (48- ALSFRS-R score at ABG)/disease duration.

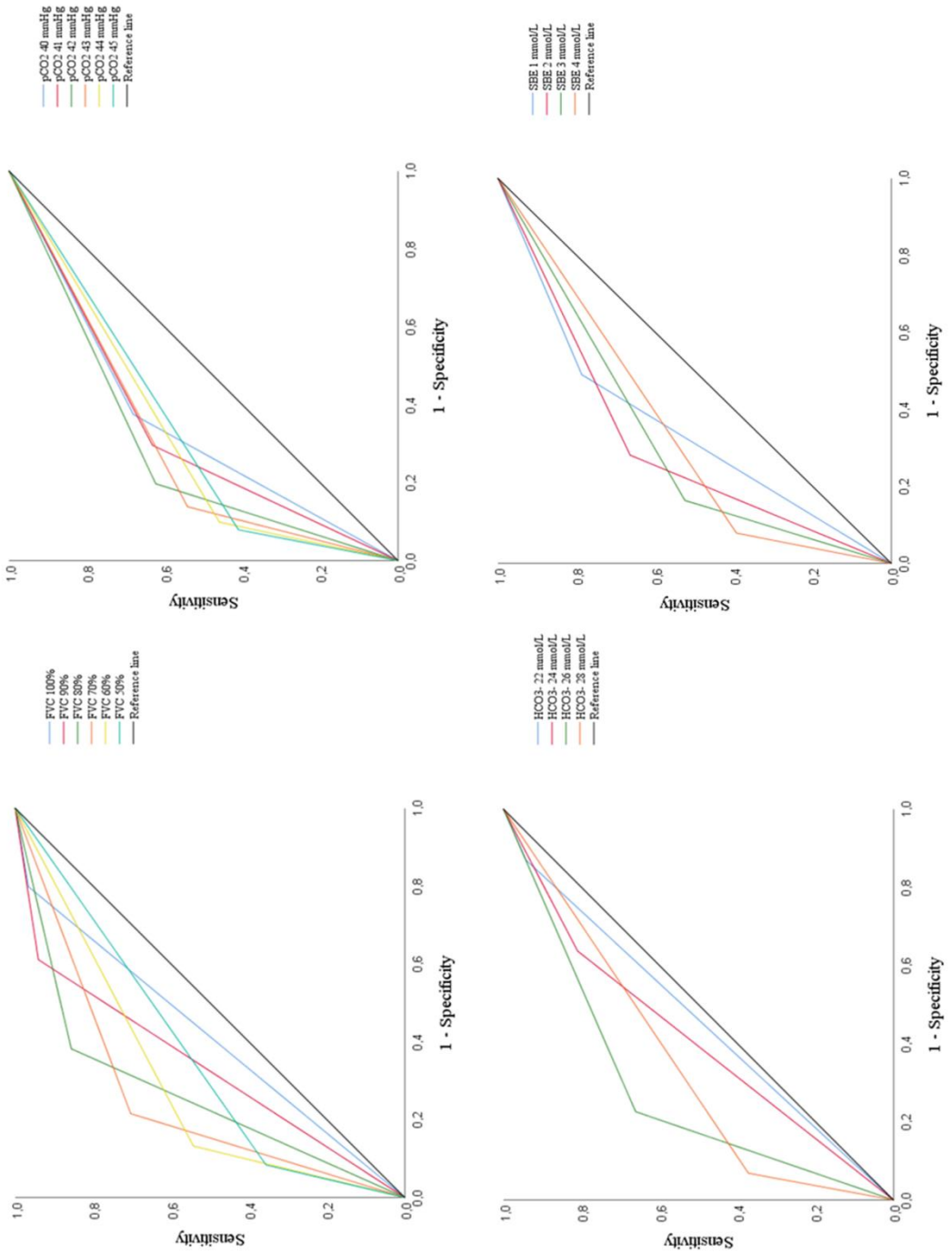
	All patients	**NIMV**	**No NIMV**	
	Median (IQR)	***Median (IQR)***	***Median (IQR)***	***p****
Age at onset (years)	66.3 (59.0-72.1)	64.9 (57.4-70.2)	68.6 (61.1-73.0)	**<0.001**
FVC (%)	75.8 (57.9-92.3)	74.6 (54.8-89.6)	79.2 (61.7-92.3)	**0.009**
FEV1 (%)	77.8 (58.5-95.6)	75.9 (56.4-93.8)	81.4 (61.3-97.1)	0.051
pH	7.43 (7.41-7.44)	7.42 (7.40-7.44)	7.43 (7.41-7.45)	**0.005**
pCO2 (mmHg)	40.0 (37.0-43.0)	40.8 (38.0-44.7)	39.0 (36.2-41.5)	**<0.001**
pO2 (mmHg)	81.0 (73.8-87.0)	80.0 (72.6-85.7)	82.1 (76.0-87.5)	**0.020**
HCO3- (mmol/l)	25.5 (23.7-27.3)	25.7 (24.0-28.0)	25.0 (23.5-26.6)	**<0.001**
SBE (mmol/l)	1.37 (-0.20-3.12)	1.66 (0.03-3.66)	0.85 (-0.54-2.65)	**0.001**
Δ ALSFRS-R (points/month)	0.55 (0.33-1.00)	0.52 (0.31-0.92)	0.62 (0.33-1.07)	0.095
Overall survival (years)	2.5 (1.7-3.8)	2.6 (1.9-4.0)	2.3 (1.5-3.5)	**0.003**
Onset-ABG/PFT interval (years)	1.1 (0.7-1.8)	1.1 (0.7-1.8)	1.1 (0.7-1.8)	0.814
ABG/PFT-death/tracheostomy interval (years)	1.2 (0.6-2.0)	1.4 (0.7-2.0)	0.9 (0.5-1.8)	**<0.001**
	n (%)	***n (%)***	***n (%)***	***p****
Sex				
Male	273 (55.9%)	166 (60.6%)	107 (50.0%)	**0.019**
Female	215 (44.1%)	108 (39.4%)	107 (50.0%)	
Type of onset				
Bulbar onset	170 (34.8%)	90 (32.8%)	80 (37.4%)	0.064
Spinal onset	318 (65.2%)	184 (67.2%)	134 (62.6%)	
Respiratory symptoms at ABG/PFT				
Dyspnea (ALSFRS-R 10 < 4)	131 (26.8%)	84 (30.7%)	47 (22.0%)	**0.032**
Orthopnea (ALSFRS-R 11 < 4)	103 (21.1%)	66 (24.1%)	37 (17.3%)	0.068
Both (ALSFRS-R 10 & 11< 4)	92 (18.9%)	61 (22.3%)	31 (14.5%)	**0.029**
No symptoms	346 (70.9%)	185 (67.5%)	161 (75.2%)	0.063
Total	488 (100%)	274 (56.1%)	214 (43.9%)	

* Significant p values (<0.05) are written in bold

eFigure1. Box-plot for median value of FVC% for different ABG parameters (pCO2, HCO3-, SBE; figures A, B, C) and for different ABG groups (figure D).



eFigure2. ROC curves for different cut-off values of FVC%, pCO2, HCO3- and SBE. Sensitivity and specificity for starting NIMV at 3 months from ABG/PFT.



eTable2. Sensitivity and specificity for NIMV starting in 3 months. Best cut-off values for FVC%, pCO2, HCO3- and SBE based on Youden Index and area under the curve (AUC). Youden Index was calculated using Youden J statistic formula (J = sensitivity + specificity – 1). The best value for each parameter are written in bold. * p-values <0.05 was considered as significant.

Parameter	Cuts-off	Sensitivity	Specificity	Youden Index	AUC	p*
FVC (%)	100	96.6%	20.0%	0.166	0.583	0.021
	90	94.1%	38.6%	0.327	0.663	<0.001
	80	85.6%	61.4%	0.470	0.735	<0.001
	70	**70.3%**	**77.9%**	**0.482**	**0.741**	**<0.001**
	60	54.2%	86.2%	0.404	0.702	<0.001
	50	35.6%	91.7%	0.273	0.637	<0.001
pCO2 (mmHg)	40.0	68.0%	62.7%	0.307	0.654	<0.001
	41.0	63.1%	70.6%	0.337	0.669	<0.001
	42.0	**62.3%**	**80.4%**	**0.427**	**0.713**	**<0.001**
	43.0	54.1%	86.3%	0.404	0.702	<0.001
	44.0	45.9%	90.2%	0.361	0.680	<0.001
	45.0	41.0%	92.2%	0.332	0.666	<0.001
HCO3- (mmol/L)	22.0	94.2%	13.0%	0.007	0.536	0.309
	24.0	81.0%	36.3%	0.173	0.586	0.015
	26.0	**66.1%**	**77.4%**	**0.435**	**0.718**	**<0.001**
	28.0	37.2%	93.2%	0.304	0.652	<0.001
SBE (mmol/L)	1.0	78.7%	51.0%	0.297	0.648	<0.001
	2.0	**66.4%**	**71.9%**	**0.383**	**0.691**	**<0.001**
	3.0	52.5%	83.7%	0.362	0.681	<0.001
	4.0	39.3%	92.2%	0.315	0.658	<0.001

eTable3. Comparison of AUC values in ROC curves (diagnostic ability of discrimination for starting NIMV at 3 months) between patients with bulbar/spinal onset and between bulbar/no bulbar dysfunction at time of ABG/PFT. No significant differences were found in AUC subdividing patients by site of onset and by bulbar involvement at time of ABG/PFT performance.

Parameter	**AUC**		**p***
	Bulbar onset	**Spinal onset**	
pCO2	0.752	0.702	0.420
HCO3-	0.761	0.716	0.466
SBE	0.755	0.709	0.458
FVC%	0.772	0.768	0.936
	Bulbar dysfunction	**No bulbar dysfunction**	
pCO2	0.691	0.770	0.180
HCO3-	0.708	0.773	0.255
SBE	0.703	0.758	0.355
FVC%	0.746	0.813	0.164

AUC: Area under the curve * p values was considered significant when <0.05.

eTable4. Hazard ratios (HR) for death/tracheostomy and NIMV starting, divided by each cut-off value for CO2, HCO3-, SBE blood levels and FVC% in patients who underwent and did not undergo NIMV. Cox proportional hazard models adjusted for sex, age at onset, site of onset (bulbar/spinal), time between onset and ABG/PFT, ALSFRS-r items 10 and 11. * p-values <0.05 was considered as significant and written in bold

	NO NIMV (n=214)		**NIMV (n=274)**			
	Risk for death/tracheostomy		**Risk for death/tracheostomy**		**Risk for NIMV**	
pCO2 cut-off	**HR (95% CI)**	**p***	**HR (95% CI)**	**p***	**HR (95% CI)**	**p***
40 mmHg	**1.362** (1.007-1.842**)**	**0.045**	1.058 (0.815-1.373)	0.674	**1.428** (1.100-1.854)	**0.007**
41 mmHg	**1.397** (1.009-1.935)	**0.044**	1.017 (0.779-1.328)	0.901	**1.352** (1.034-1.768)	**0.027**
42 mmHg	**2.227** (1.525-3.254**)**	**< 0.001**	1.110 (0.841-1.465)	0.460	**1.638** (1.233-2.176)	**0.001**
43 mmHg	**3.501** (2.266-5.410)	**< 0.001**	1.170 (0.876-1.563)	0.288	**1.815** (1.343-2.453)	**< 0.001**
44 mmHg	**3.716** (2.253-6.128)	**< 0.001**	1.026 (0.748-1.408)	0.872	**1.638** (1.184-2.267)	**0.003**
45 mmHg	**4.558** (2.586-8.035)	**< 0.001**	1.135 (0.819-1.573)	0.448	**1.704** (1.219-2.381)	**0.002**
HCO3- cut-off						
22 mmol/L	1.471 (0.959-2.256)	0.077	0.859 (0.555-1.328)	0.494	1.065 (0.680-1.668)	0.783
24 mmol/L	1.315 (0.984-1.757)	0.064	1.052 (0.788-1.403)	0.732	1.006 (0.726-1.394)	0.970
26 mmol/L	**1.509** (1.077-2.114)	**0.017**	1.123 (0.860-1.467)	0.395	**1.553** (1.181-2.040**)**	**0.002**
28 mmol/L	**2.562** (1.318-4.981)	**0.006**	1.027 (0.726-1.454)	0.880	**1.611** (1.124-2.309)	**0.009**
SBE cut-off						
1.0 mmol/L	**1.362** (1.017-1.825)	**0.038**	1.039 (0.790-1.366)	0.784	1.076 (0.797-1.452)	0.632
2.0 mmol/L	**1.555** (1.149-2.106)	**0.004**	1.071 (0.820-1.397)	0.616	**1.535** (1.177-2.000)	**0.002**
3.0 mmol/L	**1.624** (1.132-2.330)	**0.008**	1.169 (0.882-1.549)	0.277	**1.328** (1.002-1.760	**0.048**
4.0 mmol/L	**2.665** (1.660-4.278)	**< 0.001**	1.034 (0.745-1.435)	0.841	**1.476** (1.054-2.069)	**0.024**
FVC% cut-off						
100%	**1.556** (1.106-2.189)	**0.011**	0.796 (0.533-1.188)	0.264	**1.799** (1.223-2.648)	**0.003**
90%	**1.728** (1.286-2.321)	**< 0.001**	0.882 (0.627-1.241)	0.472	**2.189** (1.605-2.985)	**< 0.001**
80%	**2.147** (1.595-2.890)	**< 0.001**	1.228 (0.919-1.640)	0.165	**2.611** (1.960-3.477)	**< 0.001**
70%	**2.048** (1.505-2.789)	**< 0.001**	1.134 (0.851-1.512)	0.390	**2.920** (2.208-3.862)	**< 0.001**
60%	**1.927** (1.333-2.784)	**< 0.001**	1.146 (0.852-1.542)	0.367	**2.296** (1.666-3.164)	**< 0.001**
50%	**2.665** (1.704-4.166)	**< 0.001**	1.113 (0.799-1.550)	0.526	**1.872** (1.288-2.722)	**< 0.001**

eFigure3. Kaplan-Meier curves for median survival from time of ABG. Patients were grouped according to ABG values of pCO2 and HCO3- (pCO2 and HCO3- were considered increased if > 45 mmHg and >26 mmol/L, respectively). Patients who showed normal pCO2 and HCO3- levels showed a longer survival than patients with a single HCO3- increase (1.39 years vs 0.87 years, log-rank test p <0.001) and those with both pCO2 and HCO3- increased (0.75 years, log rank test p <0.001).